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Review

Mast cells and metabolic syndrome ☆

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ABSTRACT

Mast cells are critical effectors in the development of allergic diseases and in many immunoglobulin E-mediated immune responses. These cells exert their physiological and pathological activities by releasing granules containing histamine, cytokines, chemokines, and proteases, including mast cell-specific chymase and tryptase. Like macrophages and T lymphocytes, mast cells are inflammatory cells, and they participate in the pathogenesis of inflammatory diseases such as cardiovascular complications and metabolic disorders. Recent observations suggested that mast cells are involved in insulin resistance and type 2 diabetes. Data from animal models proved the direct participation of mast cells in diet-induced obesity and diabetes. Although the mechanisms by which mast cells participate in these metabolic diseases are not fully understood, established mast cell pathobiology in cardiovascular diseases and effective mast cell inhibitor medications used in pre-formed obesity and diabetes in experimental models offer hope to patients with these common chronic inflammatory diseases. This article is part of a Special Issue entitled: Mast cells in inflammation.

1. Introduction

Friedrich von Recklinghausen first observed mast cells as granular cells in frog mesenteries in 1863 [1]. About 12 years later, anatomist Wilhelm Waldeyer detected mast cells in a tissue spread of rat dura matter and named these cells “embryonal” or “plasma” cells [2]. In 1877, Waldeyer's medical student Paul Ehrlich stained mast cells with aniline-positive dyes in connective tissues and named them *Mastzellen*, meaning “well-fed cells” because they had high numbers of cytoplasmic granules [3]. Initially, mast cells were believed to be an important component of connective tissues and to be differentiated from fibroblasts. Their biological functions were undefined, as most studies had been limited to histological descriptions. In the 1980s, however, a growing body of evidence suggested that mast cells were actually the progeny of hematopoietic stem cells (HSC) [4,5]. Unlike other HSC offspring, such as neutrophils and erythrocytes—which circulate in the blood as mature forms—mast cells do not ordinarily circulate in mature forms. Instead, they migrate into mucosal or connective tissues, where they undergo terminal differentiation and maturation locally [6–9]. Mast cells are usually situated in the interface of host–environment (i.e., skin and mucosa), enabling them to respond rapidly to environmental stimuli.

A striking morphologic feature of mast cells is their abundance of electron-dense secretory granules containing a wide variety of mediators, such as histamine, which may increase vascular permeability and alter vascular tone. Mature mast cells release these granular mediators by explosive extrusion of mediator-containing granules, which characterizes anaphylactic degranulation [10], or by release of granular contents while retaining the granular membrane within the cytoplasma, a process called piecemeal degranulation [11]. Mast cell mediators include cytokines such as interleukin 6 (IL6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), as well as chemokines (e.g., IL8), proteases (cysteinyl cathepsins and matrix metalloproteinases [MMPs]), and cell type-specific chymases and tryptases [6,12–15]. Mast cells also can elaborate numerous lipid mediators, including prostanoids and leukotrienes. Because they can release these biologically active mediators in response to challenges with IgE and specific antigens, mast cells are traditionally considered critical effector cells in IgE-associated immediate hypersensitivity and in allergic responses such as asthma [6,16,17]. But this conventional concept is currently being modified, as recent progress has greatly broadened mast cell functions in immune responses, ranging from innate defense toward various pathogens [18] to multifaceted regulators of adaptive immune responses [19,20]. Thus, mast cells are gaining increased attention worldwide and not just limited to asthma or allergic responses.

The recent findings related to the functions of mast cells ascribe to the discovery of a mast cell-deficient mouse model ($Kit^{W/Wv}$), developed by Kitamura et al. [21]. These mice have a mutation in the white spotting W locus that encodes c-kit, the receptor for stem cell factor, which is an important cytokine for efficient mast cell development. The Kit^{W} defect is a point mutation that causes exon skipping and produces a truncated receptor; $Kit^{W/W}$ mice are not viable because of the lack of the c-kit receptor. The $Kit^{W\text{-}v}$ defect is a

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point mutation in the tyrosine kinase domain of the receptor; thus, $Kit^{W\text{-}v/W\text{-}v}$ mice have diminished Kit activity and a modest reduction in mast cell numbers. $Kit^{W/W\text{-}v}$ compound heterozygous mice—combining the severe Kit^{W} mutation with the milder $Kit^{W\text{-}v}$ mutation—have markedly reduced Kit receptor activity and are severely mast cell-deficient (~1% of normal), but they are sterile and in a mixed genetic background. These phenotypes have limited the use of these mice in mast cell biology *in vivo* studies. Another mast cell-deficient mouse model, $Kit^{W\text{-}sh/W\text{-}sh}$, was identified a few years after $Kit^{W/W\text{-}v}$ [22]. The $Kit^{W\text{-}sh}$ mutation is an inversion of a segment of chromosome 5 in the regulatory element of the Kit gene [23,24], which reduces Kit gene expression. Unlike $Kit^{W/W\text{-}v}$ mice, $Kit^{W\text{-}sh/W\text{-}sh}$ mice are fertile and in a congenic C57BL/6 background—features that greatly benefit studies of mast cells and mast cell mediators in experimental disease models. Both $Kit^{W/W\text{-}v}$ and $Kit^{W\text{-}sh/W\text{-}sh}$ mast cell-deficient mice can be corrected by adoptive transfer of *in vitro* cultured mast cells (Fig. 1). Intravenous transfer of 1×10^7 of bone marrow-derived mast cells (BMMCs) into recipient $Kit^{W\text{-}sh/W\text{-}sh}$ mice leads to mast cell correction in most organs, including the lungs, liver, spleen, lymph nodes, and stomach [25]. But the efficiency of mast cell correction depends on tissue type. By staining mast cells with connective tissue chymase mMCP-4 (mouse mast cell protease-4) polyclonal antibody, we detected comparable numbers of mast cells in atherosclerotic lesions from low-density lipoprotein receptor-deficient ($Ldlr^{-/-}$) mice and mast cell-deficient ($Ldlr^{-/-}Kit^{W\text{-}sh/W\text{-}sh}$) mice receiving 1×10^7 of donor mast cells. Complete correction of mast cells in $Ldlr^{-/-}$ $Kit^{W\text{-}sh/W\text{-}sh}$ mouse aortas restored the impaired atherosclerosis phenotypes fully to those of $Ldlr^{-/-}$ mice [26]. The same numbers of donor cells, however, corrected about 50% of KIT^{+} mast cells in adipose tissues from $Kit^{W\text{-}sh/W\text{-}sh}$ mice, which led to 50% recovery of reduced body weight in these mice [27]. This "mast cell knock-in" technique has made it possible to study specific products of mast cells in different experimental disease models [25,28]. Comparison of the phenotypes of $Kit^{W/W\text{-}v}$ or $Kit^{W\text{-}sh/W\text{-}sh}$ mice and mast cell-reconstituted $Kit^{W/W\text{-}v}$ or $Kit^{W\text{-}sh/W\text{-}sh}$ mice has revealed many *in vivo* functions of mast cells and mast cell mediators in various human disease models [26–33].

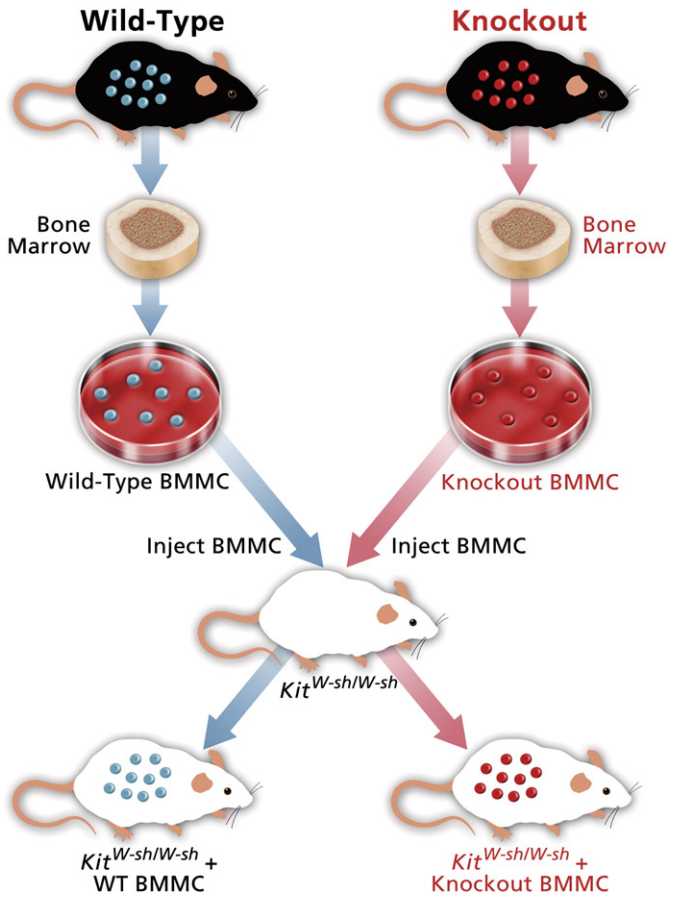

Fig. 1. Strategies for mast cell reconstitution in mast cell-deficient mice. Gene of interest knockout mouse bone marrow-derived mast cells (BMMC) were cultured in IL3 and stem cell factor and injected into tail veins of mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice to create mouse stains lacking the gene of interest only in mast cells. As a control, BMMC cultured from wild-type mice were injected into $Kit^{W\text{-}sh/W\text{-}sh}$ mice to generate wild-type mast cell-reconstituted mice in the same mouse background. This experimental procedure makes it possible to examine the molecular functions of individual mast cell gene(s) in human disease models.

Using mast cell-deficient mouse models, several groups (including our own) have revealed the roles of mast cells in cardiovascular diseases over the last few years. Degranulated mast cells were found in the interstitial myocardium in human hearts from normotensive patients [30]. Several studies showed that mast cells accumulate in human atherosclerotic plaques [34]. Recently, we reported that, compared to low-density lipoprotein receptor-deficient ($Ldlr^{-/-}$) mice, mast cell-deficient $Ldlr^{-/-}Kit^{W\text{-}sh/W\text{-}sh}$ mice in the same C57BL/6 background displayed significantly impaired atherogenesis, decreased lesion size, lipid deposition, T cell and macrophage numbers, cell proliferation, and apoptosis [26]. Greater mast cell numbers were found during heart failure; therefore, mast cells may be involved in the pathophysiology of heart failure. Hara et al. [35] used mast cell-deficient (WBB6F1/J background $Kit^{W/W\text{-}v}$) mice and their littermate wild-type control mice to demonstrate that $Kit^{W/W\text{-}v}$ mice showed reduced cardiac hypertrophy and perivascular fibrosis after aortic constriction. Abdominal aortic aneurysm (AAA), a common aortic disease in the elderly, is characterized by extensive tissue remodeling, neovascularization, inflammatory cell infiltration, and vascular cell apoptosis. A key feature of human AAA is leukocyte recruitment. Mast cells—along with neutrophils, macrophages, and lymphocytes—recently were identified in human aortic aneurysmal lesions [36,37]. Our group demonstrated that mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ mice failed to develop AAA. Adoptive transfer of BMMC from wild-type and $Tnf^{-/-}$ mice fully restored AAA formation in $Kit^{W\text{-}sh/W\text{-}sh}$ mice, but those from IL6-deficient or INF-γ-deficient mice did not—suggesting that mast cell-derived IL6 and IFN-γ, but not TNF-α , are the prime mediators from mast cells that contribute to AAA development [38].

Abdominal obesity, insulin resistance, hypertension, and dyslipidemia now are considered common risk factors for human cardiovascular diseases. More than 50 years ago, Jean Vague first described this clustering of cardiovascular risk factors as metabolic syndromes [39]. In 1988, Reaven [40] re-introduced the concept of the clustering of cardiovascular risk factors and proposed the name of Syndrome X, suggesting that insulin resistance is the dominant underlying risk factor. Several other names have been used to describe this syndrome, including "the insulin-resistance syndrome" and "the cardiovascular metabolic syndrome." In 1998, the World Health Organization proposed to use the name "metabolic syndrome" and suggested parameters and criteria for its diagnosis. According to the proposal, a person with impaired glucose tolerance (IGT) or type 2 diabetes and/or insulin resistance, together with two or more of the other components listed below, has the metabolic syndrome (Fig. 2) [41,42]:

- Abdominal obesity, defined as body mass index (BMI) $\geq$30 kg/m^2, and/or waist-to-hip ratio (WHR) >0.90 in men and >0.85 in women;
- Increased arterial pressures (>160/90 mm Hg);
- Increased plasma triglycerides (>1.7 mmol/L) and/or low levels of HDL cholesterol (<0.9 mmol/L in men, <1.0 mmol/L in women);
- Microalbuminuria (overnight urinary albumin excretion rate $\geq$20 μg/min).

In this short review, we will focus on the involvement of mast cells in metabolic syndrome.

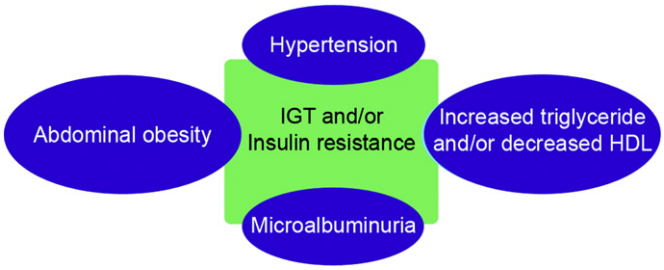

Fig. 2. Scheme of metabolic syndrome. Patients with impaired glucose tolerance (IGT) and/or insulin resistance with two or more symptoms of hypertension, abdominal obesity, microalbuminuria, and high triglyceride and/or low HDL are considered to have metabolic syndrome.

2. Mast cells in obesity

The recent worldwide obesity pandemic has gained much attention. Approximately one-third of U.S. adults are categorized as overweight or obese. Inflammation is now considered to have a pivotal role in the development of obesity. Obese adipose tissue shows the hallmarks of chronic inflammation, with massive leukocyte recruitment. Recent studies have described the accumulation of macrophages in white adipose tissue (WAT) [43,44]. Xu and colleagues compared gene expression in obese mice and in lean controls. Many macrophage-specific genes—such as MAC-1, F4/80, and CD68—are increased in WAT from obese mice; histological analysis also shows a significant increase in macrophages. Macrophage infiltration from the circulation likely explains this increase. The augmentation of chemotaxin genes, such as monocyte chemoattractant protein-1 (MCP-1), a chemoattractant specific for monocytes and macrophages, also supports this conclusion. Weisberg et al. profiled gene expression in WAT from mice with varying degrees of obesity and found that macrophage accumulation in adipose tissue is directly proportional to adiposity. Both body mass and adipocyte size were strong predictors of the percentage of F4/80 macrophages in the perigonadal, perirenal, mesenteric, and subcutaneous adipose tissue depots.

Recent studies have found that T cells also accumulate in WAT. Wu et al. [45] documented higher numbers of T cells in WAT of diet-induced obese male mice than in WAT of lean mice. Both mRNA and protein levels of RANTES, and its receptor CCR5, were increased in WAT of obese mice, suggesting that RANTES/CCR5 may be important in leukocyte accumulation. Rausch et al. [46] reported that $CD8^+$ T cells were present in large numbers within the adipose tissues of both diet-induced obese mice and genetically generated *ob*/*ob* obese mice (Fig. 3). These T cell subsets also appear in human WAT (Fig. 3). T cells and macrophages were intermittently found surrounding individual adipocytes; T cells also formed large circular clusters around where macrophages gathered. T lymphocytes cross talk with macrophages and regulate the inflammatory cascade, but their functional role in adipose inflammation remains unclear. Nishimura et al. [47] found that $CD8^+$ effector T cell infiltration precedes macrophage accumulation and contributes to macrophage recruitment. Large numbers of $CD8^+$ effector T cells infiltrated obese epididymal adipose tissue in mice fed a high-fat diet. Immunologic and genetic depletion of $CD8^+$ T cells lowered macrophage infiltration and adipose tissue inflammation, indicating that $CD8^+$ T cells are required for maintenance of the inflammatory response and that $CD8^+$ T cells have major roles in macrophage differentiation and migration. Adoptive transfer of $CD8^+$ T cells to CD8-deficient mice increased adipose inflammation, such as enhanced macrophage infiltration and IL6 and TNF-α expression in epididymal fat, and aggravated glucose intolerance and insulin resistance. In contrast to the increased infiltration of $CD8^+$ T cells, however, $CD4^+$ helper cells and T regulatory (T_{reg}) cells were strikingly reduced in obese mice [48]. Subsets of $CD4^+$ T cells secrete cytokines that can inhibit macrophage recruitment, including IL4 and IL10 [49], whereas T_{reg} cells suppress T cell, NK cell, NKT cell, B cell, and dendritic cell activities, thereby controlling adaptive immune responses [50]. Loss of T_{reg} cells with increasing adiposity, therefore, could allow an invasion of inflammatory macrophages. It remains undefined whether the influx of macrophages or the efflux of T_{reg} cells proves upstream. Both processes must be downstream of an initiating event, such as local hypoxia [51], increased death [52], and adipocyte stress [53].

Mast cells, like macrophages or T cells, are inflammatory cells, but the exact mechanisms of mast cells in the pathogenesis of obesity are not fully understood. Staining human WAT sections with a mast cell tryptase monoclonal antibody revealed high numbers of mast cells in WAT from obese subjects (Fig. 3) compared with that of lean subjects,

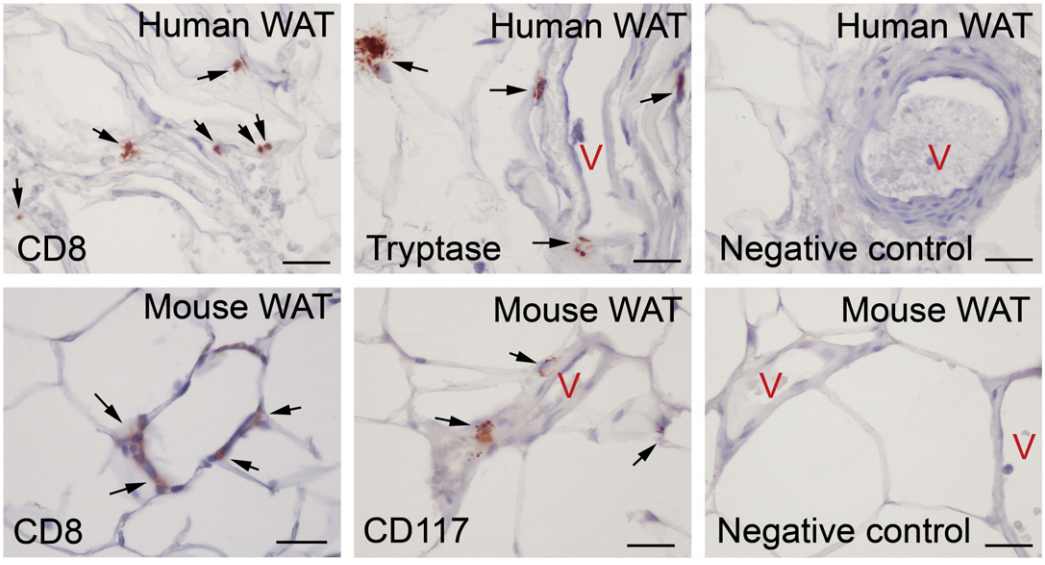

Fig. 3. $CD8^+$ T cells and mast cells in human and mouse WAT. WAT from obese humans and diet-induced obese mice were fixed for paraffin section preparation (5 μm). Human CD8 monoclonal antibody (1:75, Abcam, Cambridge, MA) and human tryptase monoclonal antibody (1:1500, Chemicon International, Billerica, MA) were used to detect human $CD8^+$ T cells and mast cells. Mouse CD8 monoclonal antibody (1:300, Abcam) and mouse CD117 monoclonal antibody (1:40, eBioscience, San Diego, CA) were used to detect mouse $CD8^+$ T cells and mast cells. Normal mouse IgG and rat IgG were used for immunohistochemical staining as negative controls for human and mouse WAT sections, respectively. Arrows indicate immunopositive cells. V = microvessel. Scale bar: 100 μm.

though WAT had fewer mast cells than macrophages [27]. Obese subjects also had significantly higher tryptase concentrations in their serum than did lean individuals. These observations suggest a possible association between mast cells and obesity [27]. Similarly, WAT from obese mice fed a high-fat diet contain higher numbers of Mac-2$^+$ macrophages [27] and CD117$^+$ mast cells (Fig. 3) than do lean controls. Direct participation of mast cells in obesity was established using mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice. *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice, fed a Western diet for 12 weeks gained significantly less body weight, had improved glucose intolerance and had reduced adipose tissue inflammation with reduced leptin and insulin levels in the circulation, compared with congenic wild-type controls. Consistently, wild-type mice receiving a daily intraperitoneal injection of the mast cell stabilizer disodium cromoglycate (DSCG) also had attenuated body weight gain. Adoptive transfer experiments of different cytokine-deficient mast cells into *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice (Fig. 1) demonstrated that mast cells contributed to diet-induced obesity by producing the inflammatory cytokines IL6 and IFN-γ. *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice receiving BMMCs from *IL6*$^{-/-}$ mice and *Ifng*$^{-/-}$ mice, but not wild-type mice or *Tnf*$^{-/-}$ mice, showed less body weight gain and improved glucose tolerance. In addition to releasing cytokines, mast cells may contribute to obesity by promoting angiogenesis. Mast cells are often localized next to microvessels in WAT (Fig. 3). The numbers of microvessels correlated with the increase in mast cell numbers during the development of obesity. WAT and muscle tissues from wild-type obese mice showed substantial immunostaining of CD31 (microvessels) and KIT (mast cells), significantly more than those from wild-type lean mice [27]. Although not tested, high numbers of mast cells in WAT from obese mice may result from enhanced mast cell proliferation, reduced mast cell apoptosis, or increased mast cell recruitment—all of which may contribute to angiogenesis in WAT. Indeed, we detected significantly higher levels of chemokine MCP-1 in WAT from obese mice than in WAT from lean mice [27]. Western diet-fed *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice or those receiving DSCG had smaller CD31$^+$ areas, similar to those from chow diet-fed lean mice. Reduced angiogenesis in *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice or those receiving DSCG resulted in high numbers of apoptotic cells in WAT and muscle tissues. Mast cells contain cell type-specific chymases and tryptases. Although there is no data to suggest that these mast cell proteases participate directly in obesity, the findings in our recent AAA study indicate that mast cell chymase plays an important role in angiogenesis. While BMMC from wild-type mice promoted microvessel sprouting in an aortic ring assay, those from chymase-deficient mice showed significantly reduced potency to microvessel sprouting [54]. Besides these cell type-specific proteases, mast cells also contain high levels of the cysteine proteases, cathepsin S, and cathepsin L [55]. Both cathepsins are critical to angiogenesis during tumor growth [56], wound healing [57], and AAA expansion (Shi, unpublished data). Indeed, WAT protein extracted from obese wild-type mice contained higher levels of cathepsins B, S, and L than that from *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice [27].

Inflammatory cells, such as macrophages, CD4$^+$ and CD8$^+$ T cells, regulatory T cells, and mast cells, all localize in WAT in humans and in mice. These observations leave many important questions to be answered. First, we ask what triggers the first inflammatory cell infiltration to WAT and which cell type appears first in WAT. Using *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice and mast cell stabilizer DSCG, we indirectly proved that mast cells infiltrate into WAT before macrophages. Inactivation of mast cells with DSCG did not affect mast cell recruitment to the WAT, but it significantly blocked macrophage accumulation in WAT [27]. We are interested in what cells trigger mast cell migration during WAT growth. Second, macrophages and mast cells interact with different T cells by many mechanisms, such as major histocompatibility (MHC) class II-mediated antigen presentation or direct release of inflammatory cytokines, which have not been studied in WAT. It is possible that macrophages and mast cells, although they are non-professional antigen-presenting cells, participate in T cell activation using the same mechanisms as those in lymphoid organs. Thus, inflammation may play a detrimental role in obesity. Third, why mastocytosis patients with excess amounts of mast cells are not always obese, although many are diabetic (R.S. Fredericks, Endocrine Associates, Reno, NV: personal communication), remains unexplained. Therefore, other mechanisms may also control body weight gain in obese patients.

3. Mast cells in insulin resistance and type 2 diabetes

Diabetes mellitus is a metabolic syndrome characterized by hyperglycemia and associated with microvascular and macrovascular complications. Type 1 and type 2 are the most common types of diabetes. Obesity is a major risk factor for insulin resistance and type 2 diabetes. Although how obesity promotes insulin resistance is unclear, the inflammatory response is thought to be a potentially important mechanism, which could alter adipose tissue function, thus leading to systemic insulin resistance. The development of insulin resistance associates with proinflammatory cytokines produced by infiltrating leukocytes and resident adipocytes within the adipose tissue in obese subjects [58]. As discussed earlier, WAT is a reservoir of different leukocytes, including macrophages, T cells, and mast cells. These cells are rich sources of proinflammatory cytokines. Hotamisligil et al. [59] and Feinstein et al. [60] showed that proinflammatory TNF-α was able to mediate insulin resistance. TNF-α is overexpressed in WAT from obese subjects. Lack of TNF-α ligand or the p55 TNF receptor improves insulin sensitivity and glucose homeostasis, suggesting that this inflammatory response is important in the regulation of insulin action in obesity [14,61–63]. The widespread use of anti-TNF-α treatment in patients with inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis yielded significant reduction of blood insulin levels and insulin/glucose index, as well as decrease of the homeostasis model assessment (HOMA) index and increase of the quantitative insulin sensitivity check index (QUICKI) among patients with high insulin resistance, supporting a role for TNF-α in systemic insulin sensitivity in humans [58,64,65]. Other inflammatory mediators and cytokines are also overexpressed in WAT, including IL6, iNOS, MCP-1, and IL1. Many of these inflammatory molecules cause insulin resistance in adipocytes [66–68].

Our work discussed earlier [27] suggested that mast cells contribute directly to insulin resistance and type 2 diabetes. Using diet-induced experimental type 2 diabetes, we demonstrated that mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice had higher insulin sensitivity and glucose tolerance than wild-type control mice on a Western diet. Wild-type mice receiving DSCG treatment also showed increases in these parameters, compared to control mice. Diabetic mice had high serum insulin and glucose levels and high numbers of KIT-positive mast cells in WAT. In contrast to many other studies, mast cell stabilization not only prevented diet-induced obesity and diabetes in mice but also had therapeutic benefit. Cromolyn (DSCG) and Zaditor (also called ketotifen), two common mast cell stabilizers used in human allergic diseases, reversed pre-established obesity and diabetes in mice. After consuming a high-fat diet for 3 months, wild-type mice became obese and diabetic. But intraperitoneal administration of DSCG or ketotifen reduced both body weight and glucose intolerance in mice that were kept on the same high-fat diet. After switching to a chow diet, obese and diabetic mice had normal body weight and glucose tolerance after 2 months of treatment with either DSCG or ketotifen—which was no different from mice that consumed a chow diet at the same ages [27]. These observations offer new hope for patients suffering from these metabolic disorders. Patients with obesity or diabetes may benefit from mast cell stabilization.

Long-term uncontrolled diabetes has numerous complications, such as neurophathy, retinopathy, nephropathy, cardiomyopathy, vasculopathy, dermatopathy, and encephalopathy [69]. The role of

mast cells in diabetic nephropathy has been extensively reviewed elsewhere [69,70] and will be only briefly covered here. Diabetic nephropathy is one of the major microvascular complications of diabetes, characterized by excessive amassing of extracellular matrix with thickening of glomerular and tubular basement membranes and increased mesangial matrix, which ultimately progress to glomerulosclerosis and tubulo-interstitial fibrosis [71]. Mast cells are found infrequently in normal kidney tissue, but mast cell infiltration is a prominent and early feature following renal injury [72]. Increased mast cell density has been noted in the kidneys of diabetic patients with nephropathy [73,74]. Mast cells participated in renal interstitial fibrosis and produced the non-fibrillar short chain type VIII collagen, suggesting that mast cells are associated with fibrosis and extracellular matrix accumulation in human diabetic nephropathy. But the mechanism by which mast cells mediate diabetic nephropathy remains unclear. Mast cell degranulation leads to the release of various mediators, such as TGF-β, chymase, tryptase, cathepsin G, rennin, and many others that may contribute to renal diseases. For instance, TGF-β is a potent profibrotic growth factor that is widely implicated in the pathogenesis of progressive renal disease [75]. Tryptase, the major mast cell enzyme, promotes renal fibroblast proliferation and collagen synthesis [76]. Chymase, a family of serine protease in mast cells, converts the biologically inactive form of TGF-β into an active form [77]. More evidence is still needed to confirm direct involvement of these mast cell-derived mediators in diabetic nephropathy.

4. Mast cells in hypertension

Hypertensive heart disease is the major cause of diastolic heart failure and other related heart diseases. Excessive myocardial fibrosis impairs cardiac function in hypertensive heart disease. Myocardial fibrosis has been described in experimental hypertension in rats [78], and it contains excessive protein deposition, mainly including type I and type III collagens [79] that may result from increased synthesis or decreased degradation of these matrix proteins. Inflammatory cell recruitment closely associates with the development of left ventricular fibrosis induced by hypertension. Hinglais et al. [80] explored the relationship between left ventricular fibrosis and inflammatory cell infiltration in spontaneously hypertensive rats (SHR). The area of fibrosis and interstitial cellular infiltrates were greater in SHR than in Wistar controls. In 12-month-old rats, fibroblasts colocalized with inflammatory cells, and the density of ED-1$^+$ macrophages and CD4$^+$ lymphocytes were increased in the fibrosis area. There were fewer CD8$^+$ cells than any other cell type (CD4$^+$ cells, macrophages, and MHC class II-positive cells) in renovascular hypertensive rats, indicating that cytotoxic lymphocytes are not greatly involved in this inflammatory process [81]. Kuwahara et al. [82,83] reported that, after a pressure overload created by a suprarenal abdominal aorta constriction, Wistar rats showed a rapid progression of marked reactive myocardial fibrosis. Using this model, they examined the role of macrophages in myocardial remodeling and cardiac dysfunction [83]. Pressure overload induced pericular macrophage accumulation, with a peak at day 3 and decreasing to lower levels by day 28. MCP-1, an important chemokine for macrophage migration, also increased after day 1, peaking at day 3 and returning to insignificant levels by day 28. Chronic treatment with an anti-MCP-1 monoclonal neutralizing antibody inhibited macrophage accumulation, suggesting that inhibition of inflammation is a new strategy to prevent myocardial fibrosis in hypertensive heart disease. Kagitani et al. administered N-(3′,4'-dimethyoxycinnamoyl) anthranilic acid (tranilast), an anti-inflammatory drug, by inhibiting lipid and inflammatory mediator release from inflammatory cells to deoxycorticosterone-acetate (DOCA) hypertensive mice. Although systolic blood pressure was similar in animals treated with tranilast or vehicle, monocyte/macrophage infiltration was suppressed, and mRNA expression of TGF-β1, type-1 plasminogen activator inhibitor, MCP-1, IL6, procollagen I, and procollagen III was attenuated. Myocardial fibrosis and collagen accumulation were also suppressed [84], suggesting that the myocardial fibrosis seen in DOCA/salt hypertensive rats associates with inflammation.

Mast cell functions in hypertension are often overlooked because of the striking features of macrophages and T cells in inflammation. Olivetti et al. [85] reported a more than three-fold increase in the numerical density of mast cell profiles in the myocardium related with capillary proliferation after pulmonary artery constriction. The interaction between mast cell number and capillary proliferation is poorly understood [86]. One possible explanation is that mast cells release heparin, which appears to be responsible for endothelial cell migration [87] and the ingrowth of new capillary units. Shiota et al. found that the density of cardiac mast cells is already significantly increased in SHRs immediately after birth. Moreover, the cardiac mast cell density was significantly higher in SHRs than in age-matched non-hyperactive Wistar–Kyoto (WKY) control rats throughout their life span. Mast cells produce TNF-α together with nuclear factor kappa-B (NF-κB) and IL6. These transcription factors and cytokines were induced significantly in prehypertensive SHRs. In the late hypertensive stage, the hearts of SHRs displayed increased areas of myocardial fibrosis, where activated mast cells are localized. The expressions of TGF-β1 and basic fibroblast growth factor (bFGF) were significantly increased in the aging and failing SHR hearts [88]. Mast cells were major sources of TGF-β1 and bFGF, although other heart cells also expressed these growth factors. Taken together, cardiac mast cells participate in the induction of cardiac hypertrophy and cardiac fibrosis by synthesizing and secreting prohypertrophic cytokines and profibrotic growth factors. Panizo et al. [89] reported that there is a positive correlation between cardiac mast cell density and the volume of the collagen fraction in the hypertrophied left ventricles of SHRs. Interestingly, Hara et al. [35] found that perivascular collagen was normal in mast cell-deficient *Kit*$^{W/Wv}$ mice after aortic banding. Recently, Levick et al. [90] identified a causal relationship between cardiac mast cells and the regulation of fibrosis in the hypertensive heart. Eight-week-old male SHRs were treated for 12 weeks with the mast cell stabilizing compound nedocromil. Left ventricular fibrosis was prevented, independent of hypertrophy and blood pressure. There are several potential mechanisms by which mast cells mediate their profibrotic actions. Mast cells produce a variety of proteases, cytokines, growth factors, and other biologically active mediators that may influence tissue remodeling. Notably, tryptase was elevated in untreated SHRs but normalized after nedocromil treatment. Tryptase is likely not the only mediator responsible; cytokines IFN-γ and IL4 were increased in SHRs and normalized by nedocromil, whereas IL6 and IL10 were decreased in SHRs, with nedocromil treatment normalizing IL6 and increasing IL10. In addition, nedocromil also prevented macrophage infiltration into the ventricle, suggesting that intercellular signaling between the inflammatory cells is important in mediating fibrosis.

5. Mast cells in dyslipidemia

Atherosclerosis is characterized by the accumulation of low-density lipoprotein (LDL)-driven cholesterol in the intima, the inner layer of the arterial wall. Macrophages uptake LDL particles, leading to the formation of foam cells. In addition to macrophages, mast cells are present in the arterial intima and are in the close vicinity of foam cells [91], suggesting that mast cells are involved in the transformation of macrophages into foam cells. As discussed, upon stimulation, activated mast cells extrude their granules into the extracellular space. There, they lose their soluble components, such as histamine, but their two neutral proteases, chymase and carboxypeptidase A, remain tightly bound to the heparin proteoglycan, thereby forming insoluble granule “remnant.” LDL binds to the heparin proteoglycan of

these mast cell granule remnants and forms insoluble complexes. These insoluble complexes are then phagocytosed by macrophages, forming macrophage foam cells [92,93]. When mast cells were activated by intraperitoneal administration of C48/80, a laboratory-use mast cell activator, LDL uptake by macrophages rose by 7–24-fold [94]. Like 48/80-triggered mast cell stimulation, IgE-dependent stimulation of sensitized mast cells also leads to increased uptake of LDL by cocultured macrophages and thereby foam cell formation [95,96]. In contrast, the mast cell stabilizer cromolyn effectively blocked mast cell-dependent LDL uptake by macrophages [95]. Along with LDL particles, high-density lipoprotein (HDL) particles constantly pass from the bloodstream into the arterial intima [91]. HDL_3 particles promote the transfer of cholesterol from the arterial intima back to the bloodstream. When mast cells are stimulated to degranulate, however, the chymase-containing granule remnants derived from degranulating rat serosal mast cells rapidly degrade the HDL_3 components apolipoprotein E (ApoE), ApoA-I, and ApoA-IV in plasma, peritoneal fluid, and possibly in atherosclerotic lesions. Thus, the net efflux of cholesterol promoted by HDL from macrophage foam cells is impaired [91,97]. Recently, Heikkila et al. [98] reported significant differences in serum lipid and lipoprotein profiles between mast cell-deficient ($Kit^{W\text{-}sh/w\text{-}sh}$) mice and wild-type mice. $Kit^{W\text{-}sh/w\text{-}sh}$ mice on an $Ldlr^{-/-}$ background have lower levels of serum total cholesterol, triglycerides, and phospholipids, thus displaying a less atherogenic lipoprotein profile. The reduction in triglycerides and phospholipids in mast cell-deficient mice may call for future studies in this important field of lipoprotein metabolism.

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